

ORIGINAL ARTICLE

Tolerance to continuous intrathecal baclofen infusion can be reversed by pulsatile bolus infusion

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Study design: Pilot study.

Objective: To study the effect of pulsatile bolus infusion of intrathecal baclofen (ITB) on daily ITB dose, in patients showing dose increases, probably due to tolerance.

Setting: Department of neurology and neurosurgery, University Medical Center Groningen, the Netherlands.

Methods: Data on dosages and clinical efficacy were gathered from four patients who were switched from continuous to pulsatile bolus infusion of ITB, because of the probable diagnosis of tolerance to ITB.

Results: Switching from continuous to pulsatile bolus infusion resulted in a decrease of the daily ITB dose, while the clinical effect could be kept stable, without introducing adverse events.

Conclusion: Pulsatile bolus infusion of ITB seems to be an effective and safe treatment strategy to reverse the need for increasing ITB dosages in patients with the probable diagnosis of tolerance to ITB.

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Introduction

Intrathecal baclofen (ITB) therapy has proven to be safe and effective in treating severe spasticity that cannot be treated optimally with oral spasmolytic therapy.^{1–3} The dose of ITB therapy has shown to increase during the first 12–18 months of therapy, very likely due to optimization of the individual needed dose, after which it stabilizes.^{2,4,5} However, unexplained dose increases may still occur in up to 20% of ITB patients after these first 18 months.^{4,6–8} These dose increases after 18 months are thought to be caused by tolerance, which is one of the major concerns of ITB therapy. Tolerance is defined as a decreasing effect during a stable dose of a drug, requiring a dose increase to produce the same previously obtained effect.⁹ The hypothesis is that tolerance in ITB therapy is induced by a reduction of the total number of GABA_B receptors, and/or by GABA_B receptor desensitization.^{10–12} The key question is how to treat tolerance in ITB therapy optimally. Altering the infusion mode from simple to complex continuous has shown not to be effective in the development of tolerance.⁸ The most advocated strategy nowadays is the drug holiday. During a drug holiday, ITB therapy is tapered off and the patient is treated with an

alternative spasmolytic drug for days to weeks, until ITB therapy is restarted.^{8,13} During this drug holiday the patient has to be monitored carefully, because of the risk of developing baclofen withdrawal symptoms.¹⁴ Although the exact mechanism behind a drug holiday is unclear, the GABA_B receptors are thought to resensitize for baclofen.

In this paper we present pulsatile bolus infusion as an alternative treatment strategy to reverse ITB dose increases, very likely due to tolerance. During the pulsatile bolus infusion mode, the ITB pump (Synchromed II; Medtronic, Minneapolis, MN, USA) is programmed to deliver the daily baclofen dose in a number of boluses (2–6 per day), instead of delivering ITB continuously.

The purpose of this pilot study was to investigate whether intermittent bolus infusion of ITB would be able to reverse the unexplained dose increases in some patients with continuous ITB infusion, without losing clinical efficacy.

Patients and methods

The departments of neurology and neurosurgery of the University Medical Center Groningen have about 70 patients treated with ITB therapy.

During the last 2 years, four patients were switched from continuous to pulsatile ITB infusion, because of the suggested development of tolerance. Tolerance was defined as an ITB dose increase of at least 100 µg during 1 year, to

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maintain a stable spasmolytic effect.⁸ Tolerance was only considered, if no other reasonable explanations, like infections and pain, could be given and after having excluded technical problems with the pump system. Because it has been reported that the ITB dose may increase during the first 12–18 months after implantation, patients were only switched to pulsatile bolus infusion after ≥ 18 months of ITB therapy.^{2,4,5,8}

Because an ITB pump cannot be stopped in between boluses, the pump was programmed to deliver the lowest possible continuous rate ('minimal infusion rate' which is $3 \mu\text{g h}^{-1}$ in case of a baclofen concentration of $1500 \mu\text{g ml}^{-1}$). The initial bolus dose was calculated as follows: ((Total Daily Dose–10%–Minimal Infusion Rate)/6). The total continuous daily dose was decreased by 10%, to be cautious, avoiding high peak concentrations from the bolus infusion. The remaining daily dose was divided over six identical boluses, with a bolus interval of 4 h. This was based on the half-life of baclofen (4–5 h) and on own clinical experience, showing a mean duration of effect after an optimal ITB bolus of about 4 h.^{15,16} The fixed bolus injection speed of the pump (Synchromed II; Medtronic) resulted in bolus durations between 3 and 5 min, depending on the magnitude of the bolus dose.

During follow-up the optimal bolus doses were adapted if necessary, with 10% increase/decrease of the previous bolus dose; an increase if the spasmolytic effect was considered to be insufficient by the patient, and a decrease if the spasmolytic effect resulted in too much hypotonia, according to the patient.

Follow-up was planned at least every 3 months, for 1 year, rating their spasticity, refilling the pump and adjusting the ITB doses if needed. The clinical efficacy of ITB was measured using the modified Ashworth scale (MAS).¹⁷ The primary end point was the mean value of the MAS scores of both knee joints. The MAS was assessed by the same investigator to rule out interrater differences.

Results

Demographics of the four patients who were switched to pulsatile ITB therapy are shown in Table 1.

Figure 1 shows the mean daily ITB dosages (bars) and the clinical efficacy (line) of four patients, with 3-month intervals, during the year before and after the switch to pulsatile ITB infusion.

Patient 1 was switched to pulsatile bolus infusion after an increase of 120 μg per day in 6 months. After the switch to

pulsatile bolus infusion, daily ITB dose was stabilized and actually dropped slightly with 20 μg per day (6%), whereas the clinical effect even improved.

Patient 2 showed a rapid dose increase from 175 to 650 μg per day in 12 months, which was necessary to keep the clinical effect stable. After switching to pulsatile bolus infusion, the daily ITB dose dropped with 84 μg per day (13%) and the MAS could be stabilized. Afterwards the ITB dose increased again slightly, but at a much lower rate.

Patient 3 showed an increase of 100 μg ITB during the 3 months before switching to pulsatile bolus infusion. After the switch to pulsatile bolus infusion, daily ITB dose initially dropped with 30 μg per day (6%) and continued to drop during the year hereafter, at the same time showing a clear improvement of the spasticity scores.

Patient 4 was switched to pulsatile bolus infusion, because the daily ITB dose was raised up to 763 μg per day during the years before. However, this dose increase was accompanied by a decrease of the clinical effect, as shown by the increased MAS, up to 4.5 points. After switching to pulsatile bolus infusion, the daily ITB dose dropped to 219 μg per day (29%) and stabilized around 474 μg per day during the first year. The clinical effect improved at the same time, as shown by the reduction of the MAS, from 4.5 to 3.5 points.

All patients experienced drop in their daily ITB dose (6–29%) after having switched to pulsatile bolus infusion. Three patients could be stabilized at this lower dose. Patient 2 only showed a slight dose increase after the switch, although at a much slower rate as compared to the year before the switch. At the same time the clinical effect was improved in three patients and remained stable in one patient (patient 2).

No correlations were found between the effect of pulsatile bolus infusion and the underlying cause of spasticity, neither with the other patient characteristics.

Discussion

Our data show that switching from continuous to pulsatile ITB infusion stabilized or decreased the daily ITB dose in all four patients, at least during the follow-up period of 12 months, whereas the clinical effect remained stable or even improved during the same period.

These are the first data showing that pulsatile ITB infusion may be considered as a useful option to treat tolerance.

Several hypotheses may explain our data

The first hypothesis is related to the dose–effect relationship of ITB. An ITB bolus may provide a better dissemination of baclofen in the cerebrospinal fluid, which correlates with higher concentrations in the spinal cord, compared to continuous infusion.¹⁸

The second hypothesis is related to receptor resensitization after pulsatile ITB infusion.¹⁹ Bolus infusions very likely cause an increase in the fluctuations of ITB concentrations over time around the catheter tip. These fluctuations may induce receptor resensitization, which could explain the reduction of the overall daily dose of ITB. Whether this hypothesis is correct will remain unclear until we have a

Table 1 Patient characteristics

Case no.	Sex	Age	Etiology	Catheter tip spinal level	Months after implantation at the moment of switching
1	M	49	MS	T10	24
2	F	22	CP	T 6	22
3	M	57	SCI	T 9	20
4	F	20	CP	T 6	37

Abbreviations: CP, cerebral palsy; MS, multiple sclerosis; SCI, spinal cord injury.

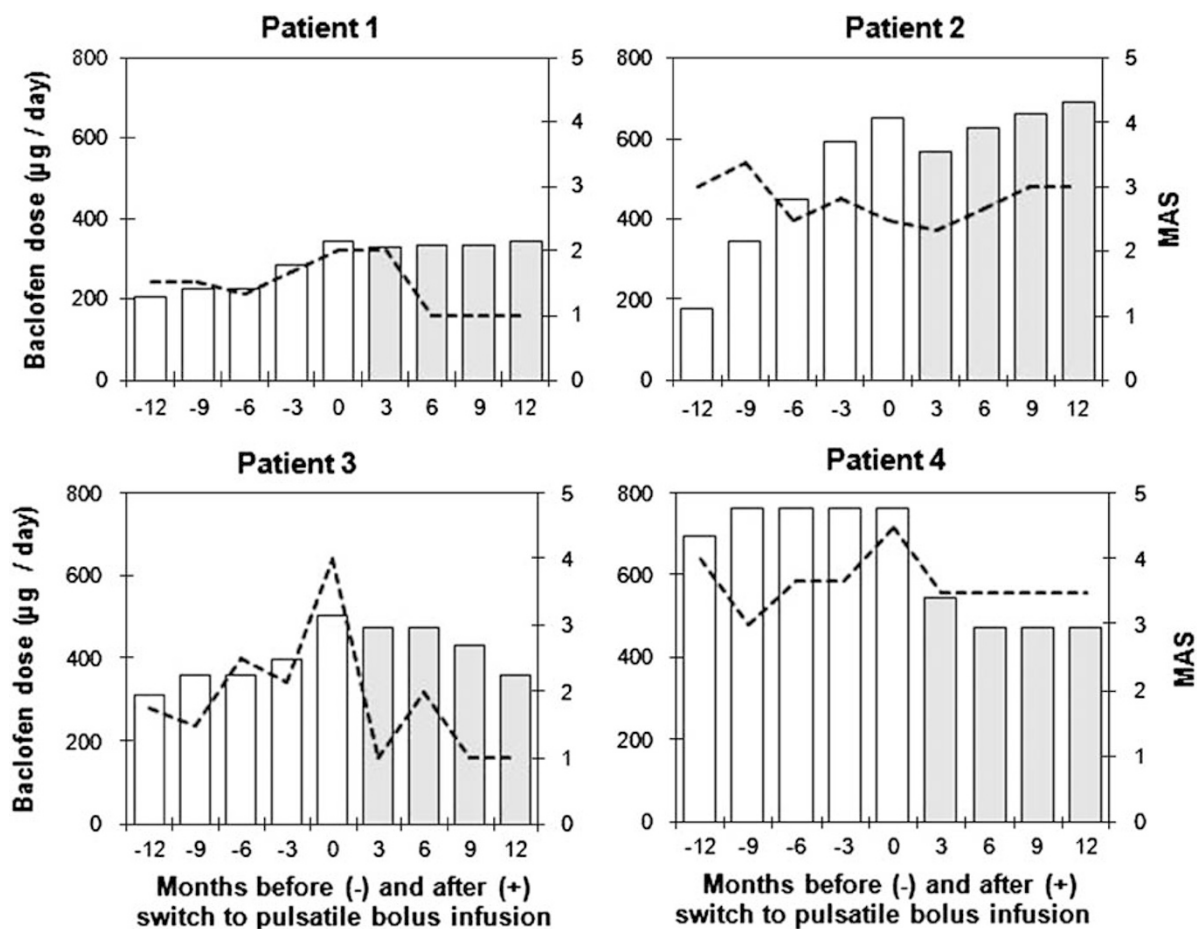


Figure 1 Daily intrathecal baclofen (ITB) dosages (bars) and Ashworth scores (dotted line) with 3-month intervals, during 1 year before (white) and 1 year after (gray) switching to pulsatile bolus infusion ($t = 0$) in four patients.

better insight into the pharmacokinetics and pharmacodynamics of ITB infusion. This is currently under investigation in our institute. Probably pulsatile bolus infusion may become even more potent by lowering the frequency of boluses per day, to provide longer periods for the GABA_B receptors to resensitize. Figure 2 shows modeled spinal ITB concentrations of two infusion regimens, consisting of a t.i.d. bolus regimen as compared to six daily bolus infusions. The concentration swings are apparently bigger in the t.i.d. regimen, which therefore theoretically could induce more resensitization. However, at this moment it is unclear if such a low-frequency ITB bolus regimen will still provide enough clinical benefit for the patients, without producing clinical wearing-off phenomena. A clinical comparison of different bolus regimens will be needed to create practical guidelines for effective infusion schedules of ITB. Based on clinical experience so far, six boluses daily, with 4 h intervals, are at least able to improve tolerance, but we do not know if this regimen is the most effective one.

Drug holiday vs pulsatile bolus infusion

Currently, the most advocated strategy to treat tolerance is a drug holiday. During this period of 2–8 weeks, baclofen

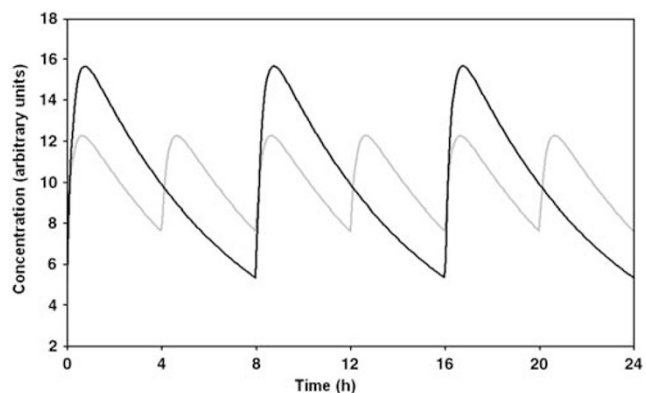


Figure 2 Comparison of the concentration/time curve of two different bolus regimens. A pulsatile bolus regimen with six boluses (gray line) and a pulsatile bolus regimen with three boluses (black line), both resulting in the same total daily intrathecal baclofen (ITB) dose (this model used an ITB half-life of 4.5 h).

therapy is tapered off and replaced by other spasmolytic medication, mostly intrathecal morphine (0.5–2 mg per day).^{13,20} During a drug holiday, hospital admission is mandatory, because of the risk of baclofen withdrawal

syndrome.¹⁴ The reported dose reduction after restarting ITB therapy varies significantly, ranging from back to initial post-implantation doses (100–200 mg per day) to even higher doses as compared to the pre-drug-holiday doses.⁶ Most patients however needed higher doses of ITB within a month after the drug holiday.

Switching to pulsatile ITB infusion does not require admission to the hospital, as there is no risk of a baclofen withdrawal syndrome.

A drug holiday can still be considered if pulsatile bolus infusion does not provide satisfactory results, but may cause significant ITB withdrawal symptoms, which makes it less attractive as first-line therapy.

Conclusion

This pilot study shows that pulsatile bolus infusion seems to be an effective and safe treatment strategy to reverse increasing ITB dosages, probably due to tolerance. Larger pharmacokinetic and pharmacodynamic studies of ITB infusion are needed to support this hypothesis and to create an optimal bolus infusion regimen for patients showing tolerance to ITB therapy.

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